STUDIES ON THE STEREOISOMERISM OF 2, 3-DIALKYL-PIPERIDINES AND PYRROLIDINES

BY

BERNARD LEROY RYDER

B. Ed., Illinois State Normal University, 1940

M. S., University of Illinois, 1947

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY IN THE GRADUATE COLLEGE OF THE UNIVERSITY OF ILLINOIS, 1952

URBANA, ILLINOIS

1952

STUDIES ON THE STEREOISOMERISM OF 2, 3-DIALKYL-PIPERIDINES AND PYRROLIDINES

BY

BERNARD LEROY RYDER

B. Ed., Illinois State Normal University, 1940

M. S., University of Illinois, 1947

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY IN THE GRADUATE COLLEGE OF THE UNIVERSITY OF ILLINOIS, 1952

URBANA, ILLINOIS

1952

ACKNOWLEDGMENT

The author wishes to express his sincere appreciation to Professor Nelson J. Leonard for his encouragement and his many valuable suggestions during the course of this investigation.

He is grateful to the Eli Lilly Company for a fellowship for the academic years 1950-1952 and wishes to thank the Research Board of the University of Illinois for their support during the summer semesters of 1951 and 1952.

The author is indebted to the Board of Trustees and the adminstrative officers of Illinois Wesleyan University for granting him a leave of absence during this period of study.

R. UNIV.
BIBLIOTHEEK
LEIDEN

PREPARATION AND STEREOCHEMICAL IDENTIFICATION OF *VICINAL*-DIALKYL- PIPERIDINES AND PYRROLIDINES

INTODUCTION

Certain alkaloids can be related structurally to *vicinal*-dialkylpiperidines by convergence of degradative and synthetic procedures, and assignment of stereochemical configuration in such an alkaloid becomes possible when the stereochemistry of the corresponding dialkylpiperidine has been determined. A notable example is the establishment of the stereochemistry of the *Cinchona* alkaloids through the aid of their correlation with the *cis* form of 3,4-diethylpiperidine (1,2). In view of the paucity of information relating the properties and stereochemical configurations of *vic.*-dialkylpiperidines, a method has been developed by which the geometrical isomers of 2-*n*-butyl-3-methylpiperidine have been separated and characterized. It is hoped that the method can be used generally for distinguishing between *cis* and *trans* forms of *vic.*-dialkylpiperidines. 2-*n*-Butyl-3-methylpiperidine wes selected for study because of the relation of this compound to the lupin alkaloids.

DISCUSSION OF RESULTS

The pure *cis* and *trans* forms of 2-*n*-butyl-3-methylpiperidine have been prepared and characterized. Isomerically pure 2-*n*-butyl-3-methylpyridine was synthesized as follows: 2-Bromo-3-methylpyridine was converted, through the lithium derivative, to 3-methyl-*a*-propyl-2-pyridinemethanol, and thence to the corresponding chloro compound, followed by reductive dehalogenation to form 2-*n*-butyl-3-methylpyridine. Isolated intermediates and the final product were characterized.

The two racemates of 2-*n*-butyl-3-methylpiperidine were obtained by the reduction of 2-*n*-butyl-3-methylpyridine. Isomer A was predominant in the sodium and ethanol reduction; isomer B was predominant in the reduction over nickel. Careful fractionation of the reduction products and further purification through derivatives served to establish the distinctness of the two isomers. Dehydrogenation of each isomer was effected over palladized asbestos at 305-310°, and it was found, in triplicate runs, that the volume of hydrogen liberated by isomer A was 60% of that liberated by isomer B. Rehydrogenation of the dehydrogenation products provided data that confirmed the results obtained in the dehydrogenation experiments.

On the basis of the dehydrogenation data for isomers A and B, together with the reported (3) dehydrogenation studies on *cis*- and *trans*-decahydroquinolines, isomer A has been assigned the *trans* configuration and isomer B has been assigned the *cis* configuration about positions 2 and 3 of the *vic.*-disubstituted piperidine.

STUDIES ON THE SYNTHESIS OF SOME *META* BRIDGED PIPERIDINES: BISPIDINE AND HOMOLOGS OF BISPIDINE

INTRODUCTION

A number of the "lupin alkaloids" are structurally related to 3,7-diazabicyclo[3.3.1]nonane, or bispidine. These include cytisine, sparteine, anagyrine and lupanine. Stereochemically, the bispidines and derivatives of bispidines possess the *cis* configuration at the centers of fusion of the *meta* bridge to the piperidine ring. These facts stimulated the study of approaches to the synthesis of the bispidines. Two approaches to the synthesis of bispidines were studied: (1) The thermal cyclization of several propane-1,1,3,3-tetracarboxamides and (2) cyclizations involving 1,5-dibromo-2,4-bis (bromomethyl)- pentane and amines.

DISCUSSION OF RESULTS

Repeated attempts to degrade propane-1,1,3,3-tetracarboxamide thermally produced only polymeric materials, rather than crystalline 2,4,6,8-bispidinetetrone, as previously reported (4). Heating a mixture of benzylamine and ethyl propane-1,1,3,3-tetracarboxylate resulted in the formation of N, N'-dibenzylmalonamide and propane-1,1,3,3-tetra-(N-benzylcarboxamide), indicated that a reversal of the Michael addition reaction had taken place. This type of degradation was believed to have taken place upon heating samples of propane-1,1,3,3-tetra-(N-methylcarboxamide) and propane-1,1,3,3-tetra-(N-ethylcarboxamide).

1,5-Dibromo-2,4-bis(bromomethyl)-pentane was prepared by a sealed-tube reaction, in which 2,4-bis(hydroxymethyl)-1,5-pentanediol was converted to the tetrabromide in the presence of hydrobromic acid. Treatment of the tetrabromide with various amines under cyclization conditions reported for the synthesis of 1-azabicyclo[2.2.1]heptane (5) did not yield the corresponding bispidines. In the case of the reaction involving methylamine, the product of the reaction mixture was believed, on the basis of infrared spectral data, to contain some unsaturated materials which might have resulted from dehydrohalogenation.

BIBLIOGRAPHY

1. V. Prelog and E. Zalán, Helv. Chim. Acta, 27, 535 (1944).
2. C. F. Koelsch and C. H. Stratton, J. Am. Chem. Soc., 66, 1881 (1944).
3. M. Ehrenstein and W. Bunge, Ber., 67, 1715 (1934).
4. M. Gutzheit and C. Jahn, J. prakt. Chem., 66, 5 (1902).
5. V. Prelog and E. Cerkovnikov, Ann., 525, 292 (1936).

VITA

Bernard LeRoy Ryder was born on April 22, 1918 at Morris, Illinois where he received his elementary and high school education. He entered Illinois State Normal University in September, 1936, and received the degree of Bachelor of Education in June, 1940. His working experience during the period 1940-1950 included public high school teaching, industrial chemical experience, and college instruction in chemistry at Illinois Wesleyan University. During that period he entered the Graduate College of the University of Illinois and received the Master of Science degree in August, 1947.

He held the Eli Lilly Fellowship in Chemistry for the academic years 1950-1952, a University of Illinois Fellowship during the summer semester of 1951, and a half-time research assistantship during the summer semester of 1952.